

Side effects of amrinone therapy

Sir,

In a recent paper, Wilmshurst and Webb-Peploe¹ wrongly attribute to us the claim that the improvement in left ventricular performance produced by amrinone is predominantly due to its positive inotropic action. This assertion cannot, however, be found in our paper² quoted by Wilmshurst. Indeed, when investigating an agent with both inotropic and vasodilator properties it is extremely difficult to ascertain the relative roles of these two mechanisms in increasing cardiac performance. Thus, we have taken great care in all of our papers²⁻⁵ to state that both actions of amrinone were likely to be implicated in the haemodynamic improvements observed and not to comment any further. This, we think, represents a fair assessment of the situation and the present consensus, given that in contrast to many investigators^{2-6,7} Wilmshurst *et al.*⁸ are the only ones who have failed to observe the positive inotropic action of amrinone.

Thierry H LeJemtel,
Albert Einstein College of Medicine,
Yeshiva University,
New York 10461.

References

- 1 Wilmshurst PT, Webb-Peploe MM. Side effects of amrinone therapy. *Br Heart J* 1983; 49: 447-51.
- 2 LeJemtel TH, Keung E, Ribner HS, *et al.* Sustained beneficial effects of oral amrinone on cardiac and renal function in patients with severe congestive heart failure. *Am J Cardiol* 1980; 45: 123-9.
- 3 LeJemtel TH, Keung E, Sonnenblick EH, *et al.* Amrinone: a new non-glycosidic, non-adrenergic cardiotonic agent effective in the treatment of intractable myocardial failure in man. *Circulation* 1979; 59: 1098-104.
- 4 LeJemtel TH, Keung EC, Schwartz WJ, *et al.* Hemodynamic effects of intravenous and oral amrinone in patients with severe heart failure: relationship between intravenous and oral administration. *Trans Assoc Am Physicians* 1979; 92: 325-33.
- 5 Siegel LA, Keung E, Siskind SJ, *et al.* Beneficial effects of amrinone-hydralazine combination on resting hemodynamics and exercise capacity in patients with severe congestive heart failure. *Circulation* 1981; 63: 838-44.
- 6 Benotti JR, Grossman W, Braunwald E, Davolos DD, Alousi AA. Hemodynamic assessment of amrinone: a new inotropic agent. *N Engl J Med* 1978; 299: 1373-7.
- 7 Cardenas M, Vidaurri A. Estudio de los efectos hemodinámicos de diferentes dosis de un nuevo inotrópico la amrinona. *Arch Inst Cardiol Mex* 1979; 49: 961-8.
- 8 Wilmshurst PT, Thompson DS, Dittrich HC, *et al.* Effects of intravenous and intracoronary amrinone in congestive cardiac failure [Abstract]. *Circulation* 1982; 66 (suppl 2): 137.

This paper was shown to the authors, Dr Wilmshurst and Dr Webb-Peploe, who reply as follows:

Sir,

In the paper by LeJemtel *et al.*¹ the cardiotonic efficacy of amrinone is mentioned in the abstract but vasodilatation is not, the introduction is devoted entirely to the positive inotropic effects of the drug with no mention of vasodilatation, and in the discussion the vasodilator properties are mentioned in only one paragraph, while the effects of the drug on contractility are discussed in five paragraphs. The paragraph summarising the results and conclusions discusses this "cardiotonic agent" without mention of vasodilatation. In the most recent publication by the same authors² they state that "amrinone, a non-glycosidic, nonadrenergic cardiotonic agent, improves ventricular performance and reduces symptoms"; they do not describe amrinone as a vasodilator and cardiotonic agent. We fail therefore to see how we could have misrepresented the message in the paper by LeJemtel *et al.*¹ and would suggest that he has altered his views somewhat since he wrote that paper. LeJemtel's letter suggests that in their paper¹ they showed a positive inotropic effect with amrinone. This is difficult to accept since they did not measure any indices of contractility.

It is true that some of our work³⁻⁶ with amrinone contrasts with that of other workers who have measured contractility indices in patients with heart failure,⁷⁻⁹ but we point out that in each case the studies reported by others were considerably smaller than our own. The total number of observations in these studies⁷⁻⁹ combined was less than that in one of our own studies.⁴ It is interesting that despite small numbers of observations in the studies in question⁷⁻⁹ the authors report a positive inotropic effect in patients with the drug at doses which have little or no inotropic effect in normal animals in which acute heart failure had been induced.¹⁰

In isolated muscle bath experiments using both human⁶ and animal tissues,¹¹ under conditions in which it is possible to measure any direct inotropic

effect since preload and afterload are carefully controlled, there is good evidence that with advancing degrees of chronic cardiac failure amrinone exerts less and less of a positive inotropic effect.

Finally, in none of the papers cited by LeJemtel was a dose response relation established for the positive inotropic effects in man.

We believe that these studies illustrate the dangers of starting out with a preconceived notion of a drug's action and attempting to confirm it using a faulty experimental design.

P T Wilmshurst,
M M Webb-Peploe,
St Thomas's Hospital,
London SE1 7EH.

References

- 1 LeJemtel TH, Keung E, Ribner HS, *et al.* Sustained beneficial effects of oral amrinone on cardiac and renal function in patients with severe congestive heart failure. *Am J Cardiol* 1980; 45: 123-9.
- 2 Maskin CS, Sinoway L, Chadwick B, Sonnenblick EH, LeJemtel TH. Sustained hemodynamic and clinical effects of a new cardiotonic agent, WIN 47203, in patients with severe congestive heart failure. *Circulation* 1983; 67: 1065-70.
- 3 Wilmshurst PT, Thompson DS, Jenkins BS, Coltart DJ, Webb-Peploe MM. Haemodynamic effects of intravenous amrinone in patients with impaired left ventricular function. *Br Heart J* 1983; 49: 77-82.
- 4 Wilmshurst PT, Thompson DS, Ditttrich HC, *et al.* Effects of intravenous and intracoronary amrinone in congestive cardiac failure [Abstract]. *Circulation* 1982; 66 (suppl 2): 137.
- 5 Wilmshurst PT, Thompson DS, Miles CM, *et al.* Comparison of the acute effects of amrinone and nitroprusside on haemodynamics and myocardial metabolism in patients with left ventricular failure. *Clin Sci* 1983; 65: 26P.
- 6 Wilmshurst PT, Walker JM, Fry CM, *et al.* The inotropic and vasodilator properties of amrinone on isolated human tissue. *Clin Sci* 1983; 64: 7P.
- 7 Benotti JR, Grossman W, Braunwald E, Davolos DD, Alousi AA. Hemodynamic assessment of amrinone: a new inotropic agent. *N Engl J Med* 1978; 299: 1373-7.
- 8 Cardenas M, Vidaurri A. Estudio de los efectos hemodinámicos de diferentes dosis de un nuevo inotrópico: la amrinona. *Arch Inst Cardiol Mex* 1979; 49: 961-8.
- 9 Jennings K, Gwilt D, Crean P, Turnbull S, Gold R, Julian DG. The clinical cardiovascular pharmacology of amrinone. A selective cardiotonic agent. *Acta Cardiol (Brux)* 1982; 28: 67-75.
- 10 Satoh K, Maruyama M, Taira N. The improvement of cardiac performance by amrinone, a new cardiotonic drug, in an experimental failing heart preparation of the dog. *Jpn Heart J* 1982; 23: 975-80.
- 11 Gaide MS, Fitterman WS, Wiggins JR, Myerburg RJ, Cameron JS, Bassett AL. Amrinone relaxes potassium-induced contracture of failing right ventricular muscle of cats. *J Cardiovasc Pharmacol* 1983; 5: 335-40.